REMARKS

In an Office Action dated September 12, 2008, Examiner Chunduru: (1) rejected claims 2, 20, 23-28, 33-35, 37, 39-40, 43, and 45-48 as anticipated by U.S. Patent 6,346,386 to Elenitoba-Johnson ("Elenitoba-Johnson"); rejected claims 3,18-19, 29-30, 33-35 as obvious over Elenitoba-Johnson in view of U.S. Patent No. 6,927,027 to Erikson et al. ("Erikson"); (3) rejected claims 65-66 as obvious over Elenitoba-Johnson in view of Nurmi et al. ("Nurmi"); and found that claims 24, 49-50, 53, 55-58, and 61 are subject to nonstatutory obviouness-type double patenting in view of claims 1-2 of U.S. Patent No. 7,387,887 to Wittwer et al. (the "Wittwer Patent"). In response, Applicant has amended claims 24, 26, 28, 29, 30, and 45 as discussed below; offers new claims 83-86 as discussed in an examiner interview dated December 18, 2008; and offers the remarks below with regard to the remaining rejections.

I. Clarifying Amendments.

Claim 24 has been amended to incorporate the subject matter of claim 3. Claims 29 and 30 have been amended for consistency with the amendment to claim 24. Claim 45 has been amended to clarify that normalizing the melting curve is normalizing magnitude differences of the melting curve. Support for this amendment is found in paragraph 0161 of the published application. Claims 26, 28, 46, and 48 have been amended to clarify that the fluorescence difference between the normalized curves is plotted by selecting the melting curve as the standard and it is plotted as zero across temperatures, and the melting curve for each additional target nucleic acid is plotted as a difference from the standard across all temperatures. Support for this amendment is found in the specification in paragraphs 0034 and 0163 of the published application and in Figs. 12C-D. Claim 49 has been rewritten in independent form. Claim 49 has also been amended to clarify the meaning of the "wave like" notation. Support for this amendment can be found in the specification, illustratively in paragraph 0068 of the published application. No new matter has been added by way of these amendments. Claim 85 has been added, wherein it is identified that an analysis of melting curves is made without creating a derivative curve. Support for this amendment can be found in the specification, illustratively in paragraph 0028 of the published application.

Claims 2-3 have been cancelled.

II. The Elenitoba-Johnson Patent does not anticipate claims 2, 20. 23-28, 33,-35, 37, 39-40, 43, 45-48.

Claims 2, 20, 23-28, 33,-35, 37, 39-40, 43, 45-48 have been rejected as anticipated by the Elenitoba-Johnson Reference.

A. Amended Claim 24 incorporates the limitations of non-rejected claim 3.

Claim 2 has been cancelled. Claim 24 has been amended to incorporate the limitations of claim 3. Since the examiner did not find claim 3 to be anticipated by the Elenitoba-Johnson Patent, and amended claim 24 now incorporates the subject matter of claim 3, independent claim 24 clearly includes limitations not disclosed in Elenitoba-Johnson. Further, since claims 20, 23-28, 33-35, 37, 39-40, and 43 depend from independent claim 24, and incorporate all the limitations therein, applicants respectfully request withdrawal of this rejection as it applies to these claims.

B. Claims 45-48 are not Anticipated by Elenitoba-Johnson.

As discussed in an examiner's interview dated December 18, 2008, the Elenitoba-Johnson Reference does not disclose the normalization of melting curves as part of PCR analysis. With respect to claims 45-48, the Examiner cites to col. 3, lines 6-67; col. 4, lines 1-67; col. 5, lines 1-5, and col. 6, lines 35-54, and col. 7, lines 18-30 of Elenitoba-Johnson in support of a finding that normalization of melting curves is disclosed therein. However, in no section of Elenitoba-Johnson is a single normalized melting curve shown or taught, and there is no teaching or suggestion to compare multiple several normalized melting curves.

Specifically, Col. 3, particularly lines 41-50, of Elenitoba-Johnson describe comparing the melting point, presumably the Tm, of a known wild-type sample sequence to an unknown "segment of interest." While this section discusses comparing the differences between melting temperatures of a known versus an unknown sequence segment, there is no discussion whatsoever of magnitude differences in fluorescence between melting curves or of a normalized melting curve. Instead, as is consistent throughout the Elenitoba-Johnson Reference, Col. 4, lines 10-17 describe melting peaks shown in derivative plots. Further, Col. 4, lines 41-50 discuss Fig. 1, showing the predicted melting temperatures of various melting domains of the N-RAS exon 2 fragment. This is not a melting curve, nor is there any disclosure of a normalized melting curve. Additionally, col. 5, lines 1-5 discuss the inset graph in Fig. 2, which is the only actual melting curve shown or discussed in Elenitoba-Johnson (others are derivative plots). While the inset in Fig. 2 compares two melting curves,

as can be seen in the y-axis, both curves show absolute fluorescence, and, thus, are not normalized to compensate for magnitude differences between samples. Applicants respectfully request the examiner to compare the inset in Fig. 2 of Elenitoba-Johnson to the raw melting curves shown in Fig. 12A of the present application and to the normalized melting curves shown in Fig. 12B of the present application.

Claim 45, requires normalization of the curves, and as discussed, Applicants have amended claim 45 to further clarify that the normalization relates to the magnitude differences between the melting curves. In fact, the present specification teaches several ways to normalize melting curves, including those discussed in paragraphs 0161 and 0165 of the published application. This normalization is not taught or suggested anywhere in Elenitoba-Johnson. Likewise, col. 7, lines 18-30 of Elenitoba-Johnson discuss derivative plots, with no suggestion whatsoever of a normalized melting curve. Col. 6, lines 35-54 discusses dyes that may be used, but does not reveal the specifics of any melting curve analysis. As claim 45 is not anticipated by Elenitoba-Johnson, applicants respectfully request withdrawal of this rejection with respect to claims 45-48, as discussed in the examiner interview of December 18, 2008.

III. Claims 3, 18-19, 29-30, 33-35 are not obvious over Elenitoba-Johnson in view of Erikson (U.S. Patent No. 6,927,027).

Claims 3, 18-19, 29-30, 33-35 stand rejected under 35 U.S.C. § 103(a) as being obvious over Elenitoba-Johnson in view of Erikson (U.S. Patent No. 6,927,027). According to the Examiner, Elenitoba-Johnson teaches a method of PCR analysis, as discussed above. However, the Examiner acknowledges that Elenitoba-Johnson "did not specifically teach saturating dyes as claimed in claims 29-30, excitation and emission maximum in a range of 410-465 nm and 450-500 nm.

As an initial matter, applicants note that not all of the dyes listed in claims 29-30 have excitation and emission maxima in the range of 410-465 nm and 450-500. Applicants respectfully refer the Examiner to Table 1 of the specification, page 19 of the published application. It is noted that the subject matter of claims 18-19 is distinct from the subject matter of claims 29-30.

Turning to claims 18-19, the Examiner notes that Erikson teaches the excitation and emission wavelength of the dyes ranging from 200 to 1000 nm. However, there is nothing in Erikson that teaches using a fluorimeter having the specific excitation range of 450-490 nm and detection range of 510-530 nm, to excite and detect a dye having an excitation maximum in the range of 410-465 nm (which only slightly overlaps the fluorimeter excitation range) and an emission maximum in the range of 450-500 nm (which does not overlap at all the detection range of the fluorimeter). Applicants respectfully note that claims 18-19 require both a fluorimeter having the defined ranges and a dye having excitation and emission maxima in a different set of defined ranges. Such is not taught or suggested in the combination of Elenitoba-Johnson and Erikson. Applicants respectfully request withdrawal of this rejection with respect to claims 18-19.

Turning to claims 29-30, both of these claims depend from claim 24. As amended, claim 24 requires a dsDNA binding dye having a percent saturation of at least 90%, amplifying the presence of the dye, and identifying the genotype using the shape of a melting curve. Elenitoba-Johnson was able to identify certain genotypes in derivative curves by using a GC-clamp, which creates two melting domains (col. 3, lines 6-13). Elenitoba-Johnson was able to exploit the GC-clamp in this manner with SYBR Green I and YO-PRO-1. While YO-PRO-1 does have a fairly high percent saturation, SYBR Green I has a percent saturation below 50%. Thus, there is no suggestion in Elenitoba-Johnson to choose dyes having a high percent saturation. Erikson teaches methods for forming multiplexes, comprising three or four strands of nucleic acid. Erikson does not suggest which dyes might be suitable for use in PCR and post-PCR melting. Applicants respectfully submit that the combination of Elenitoba-Johnson and Erikson do not suggest any particular dyes that may be used in the method of claim 24. Accordingly, applicants respectfully request withdrawal of this rejection as it applies to claims 29-30.

With respect to claim 33, the Examiner cites Erikson, col. 16, lines 47-63 for disclosure of probe-target binding. However, this section discloses using a probe to form a triplex formation. In other words, this a single-stranded probe that is hybridized to a double-stranded target. Such is incompatible with amplification.

With respect to claim 35, as discussed above, Elenitoba-Johnson uses a GC-clamp to create two melting domains in the amplicon. It is this GC-clamp that allows heteroduplex

detection in the lower melting domain. Claim 35 specifically requires that the target nucleic acid have only one melting domain.

Applicants respectfully request withdrawal of this rejection.

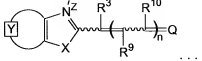
IV. Claims 65-66 are not obvious over Elenitoba-Johnson in view of Nurmi (Anal. Biochem., Vol. 299, pp. 211-217, December 2001).

Claims 3, 18-19, 29-30, 33-35 stand rejected under 35 U.S.C. § 103(a) as being obvious over Elenitoba-Johnson in view of Nurmi. According to the examiner, Elenitoba-Johnson teaches a method of PCR analysis as discussed above, but does not teach target nucleic acid as a locus of HLA gene. The Examiner notes that Nurmi teaches PCR analysis of a ds binding dye and a probe, wherein the method comprises a target nucleic acid comprising the HLA gene.

Claims 65-66 depend from claim 24, which has been amended to require a dsDNA binding dye having a percent saturation of at least 90%. Neither Elenitoba-Johnson nor Nurmi teach such a dye. Moreover, there is absolutely no discussion whatsoever in Nurmi regarding melting curves, as required by the present claims. Furthermore, the amplification curves that are compared in Nurmi are generated using a labeled probe, not a dsDNA binding dye. While ethidium bromide is used, this dye is used only as a positive control, to show that amplification has occurred. Nurmi does not teach comparing curves generated from ethidium bromide. Applicants respectfully request withdrawal of this rejection.

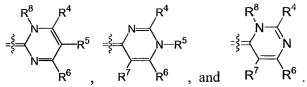
V. Non-Statutory Double Patenting.

The examiner has rejected claims 24, 49-50, 53, 55-58, and 61 as being subject to non-statutory double patenting in view of claims 1-2 of U.S. Patent No. 7,387,887 to Wittwer et al. (the "Wittwer Patent"). However, Applicants respectfully note that claims 1 and 2 of the Wittwer Patent are directed toward a PCR reaction mixture including a dsDNA binding dye having the formula:



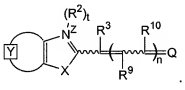
. . .

and wherein Q is selected from the structures:

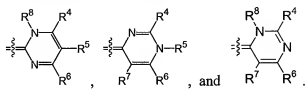


Where R4 is selected from the group consisting of arylcarbonylthio, cycloheteroalkylcarbonylthio, dialkylaminoalkylcarbonylthio, cycloalkylthio, cycloheteroalkylthio, trialkylammoniumalkylthio, and nucleosidylthio, each of which may be optionally substituted . . . .

Conversely, the present claim 49 is directed to a method of PCR analysis using a dsDNA binding dye having the formula:



and wherein Q is selected from the structures:



Wherein R4 is independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, alkenyl, polyalkenyl, alkynyl, polyalkynyl, alkenylalkynyl, aryl, heteroaryl, alkoxy, alkylthio, and dialkylamino, each of which may be optionally substituted; an acyclic heteroatom-containing moiety or a cyclic heteroatom-containing moiety; a BRIDGE-DYE; and a reactive group; each of which optionally includes a quaternary ammonium moiety . . . .

Therefore, the chemical structures of the dsDNA binding dye of claim 49 differs from that claimed in claims 1 and 2 of the Wittwer Patent. Further, the remaining claims depend from claim 49, with the exception of claim 24. As discussed above, claim 24 has been amended to include the limitation of a dye having a percent saturation of at least 90%. Therefore, Applicants respectfully submit that each of the claims are patentably distinct from claims 1 and 2 of the Wittwer Patent, and respectfully request reconsideration of this rejection.

VI. Claims 49-51, 53, 55-58 are not indefinite.

The Examiner had maintained the rejection of claims 49-51, 53, and 55-58 as indefinite under 35 U.S.C. 112, second paragraph. In the previous action, the Examiner found these claims to be indefinite due to the use of "wave like" notation. Applicants submitted that the nature of the bonds suggested by the "wave like" lines is discussed in paragraph 68 of the present application, noting that the bonds and charge at each atom are tautomeric in nature, and will exist in several forms in equilibrium. Although this notation is defined in the specification such that one of ordinary skill in the art can determine the structure of the molecule described, the examiner has maintained this rejection, stating that limitations from the specification are not read into the claims. Although applicants maintain that the specification provides a suitable definition of this term, in an effort to advance prosecution of this matter, applicants have defined the wave-like notation in claim 49. Claims 50-51, 53, and 55-58 depend therefrom.

Applicants respectfully request withdrawal of this rejection.

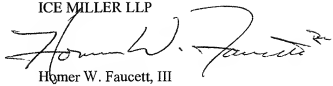
Conclusion

Applicants have overcome the examiner's rejections, and respectfully request allowance of the claims for the reasons above. In the event Applicants have inadvertently overlooked the need to petition for an extension of time or to pay an additional fee, Applicants conditionally petition therefor, and authorize any fee deficiency to be charged to deposit account 09-0007. When doing so, please reference the above-listed docket number.

If the Examiner has any questions, please contact the undersigned.

Respectfully submitted,

ICE MILLER LLP



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